

cumb to non-tuberculous diseases, and while applying the tuberculin test to apparently healthy individuals. These tests have shown conclusively that practically every person living in a large city has been infected with tubercle bacilli during his or her childhood, though not everyone has become sick with the disease as a result of this infection. It has also been found that tuberculous infection immunizes the individual against exogenic reinfection or super infection with the same virus. For these reasons the unaffected consort of a phthisical person, having been infected with tubercle bacilli during childhood, cannot be reinfected through intimate contact with a phthisical partner. Whether the unaffected consort shall develop phthisis depends on entirely other factors.

The bearings of these findings on our practical application of prophylactic measures in tuberculosis are clear.

THE STATUS OF DIPHTHEROIDS WITH SPECIAL REFERENCE TO HODGKIN'S DISEASE.

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(From the Pathological Laboratory, Roosevelt Hospital, New York, 1914-1916.)

At the present time Hodgkin's disease is quite generally believed to be a specific infection, bacterial or protozoan in origin, but for many years it was a debated question whether it was a malignant new growth or a peculiar form of tuberculosis.

In 1884, Weigert¹ demonstrated in glands of this condition organisms resembling the bacillus of tuberculosis, and in 1898 Sternberg² published his extensive monograph, treating Hodgkin's disease as a form of tuberculosis. At this time undoubtedly many cases of tuberculosis, lymphosarcoma, and peculiar hyperplasias were described under this heading, for Sternberg wrote "that many cases of so-called Hodgkin's disease, in which by animal experimentation lymphosarcoma had been ruled out, would be of this tuberculous type." This was based on the finding of tubercle bacilli or their results in glands or in some other part of the body in 15 cases with autopsy. Partly confirming this, Reed,³ in 1902, injected three animals with gland emulsions; one became tuberculous and the other two showed negative findings. Sternberg,⁴ in 1905, realized this dual pathology as coincidental. Why these two conditions

¹ Quoted, Fabian: *Centralbl. f. allg. Path. u. Path. Anal.*, 1911, xxii, 145.

² *Ztschr., f. Heilkunde*, 1898, Bd. xx.

³ *Johns Hopkins Hosp. Rep.*, 1902.

⁴ *Path. d. Primärerkrankungen d. Lymphat. u. Hämatopoetischen Apparates*, 1905.

were so commonly associated at that time is unexplained, for none of the late reports show this complex. In not one of the glands of a series just reported by the author³ is the picture suggestive of tuberculosis.

Among the early researches on the bacteriology of Hodgkin's disease in this country were those of White and Proseher.^{6,7,8} These writers separately and in collaboration demonstrated spirochetes in large numbers in 4 cases of Hodgkin's disease, in 1 case of leukemia, and in 1 of lymphosarcoma. In this latter case a gland emulsion injected into a guinea-pig, caused in two months, at the site of inoculation an ulcer, with enlarged glands in the groin. Spirochetes were demonstrated in large numbers in both these lesions. Staphylococci and streptococci may give rise to a picture simulating Hodgkin's disease histologically, either by direct infection or as an irritative reaction.

Jacobsthal,⁹ in 1908, found in one case a granular rod not differentiated from the tubercle bacillus. This was injected into a guinea-pig and caused a transitory lymph-gland enlargement. In 1910 Fränkel and Mueh¹⁰ reported 10 cases of Hodgkin's disease definitely non-tuberculous, in 9 of which they found by the antiformin treatment of glands, a granular rod non-acid fast. The demonstration was made by Mueh's modification of Gram's stain. In 5 cases of lymphatic leukemia, by the same method, they found a similar organism. Fränkel¹¹ in a later communication said these rods were very scanty, sometimes a *three days' search being necessary to find them in tissue*. Bunting in his cultural work refers to this point. Hirschfeld,¹² Rosenfeld,¹³ Dietrich,¹⁴ Simonds,¹⁵ and Luce¹⁶ have each reported the finding of granular rods in malignant lymphoma in sections, and by the antiformin method. Sticker and Lowenstein¹⁷ have implanted this tissue in pigs and obtained granulomata with and without tubercle bacilli.

Negri and Mieremet,¹⁸ in 1913, published the morphological and cultural characteristics of a diphtheroid organism similar to that described by Fränkel and Mueh, obtained from the glands of malignant granuloma. In tissue it appeared as a Gram-positive non-acid-fast granular rod 1.3×0.8 μ ., with rounded ends and central constriction. Cultivation on such media as Bordet, Loeffler, and glycerin-phosphate-potato-agar gave the following forms:

1. Short plump rods, 1×0.75 μ ., with many coccoid forms.
2. Small slender rods, 1.5 to 2×0.75 μ .

³ Cunningham: *AM. JOUR. MED. SC.*, 1915, cl, 868.

⁴ *Jour. Am. Med. Assn.*, August 13, 1907, xlix.

⁵ *Ibid.*

⁶ *München. med. Wchnschr.*, 1910, xiii, No. 1035.

⁷ *Ibid.*, 1911, Part I, lviii, 1266.

⁸ *Folia Haemat.*, 1910, Part I, x, 67.

⁹ *Berl. klin. Wchnschr.*, 1911, xlviii, 2196.

¹⁰ *Folia Haemat.*, 1912, xiii, 43.

¹¹ *München. med. Wchnschr.*, lviii, Part I, 1266.

¹² *Centrallbl. f. Bact.*, xv, 267.

¹³ *Ibid.*, p. 1115.

¹⁴ *Ibid.*, p. 685.

¹⁵ *Ibid.*

¹⁶ *Ibid.*, 1913, lxxviii, 292.

3. Small rods 2 to 3 m. long with pale granules. These predominated on old Loeffler media.

4. Granular rods, 5 to 7 m. long and 0.75 to 1.5 m. wide.

5. Involution forms.

In large doses these organisms were non-pathogenic to guinea-pigs and caused only a transitory lymph-gland enlargement in the ape (probably irritative hyperplasia). These writers gave it the name *Corynebacterium granulomatosis maligni*.

Bunting and Yates,¹⁹ in 1913, in a preliminary contribution, reported a pure culture of a Gram-positive, non-acid-fast, pleomorphic diphtheroid organism isolated from 4 cases. In later works^{21 22 23} complete details of the morphological and cultural characteristics and animal inoculation were described. The organism grew well on Dorset's egg media and glycerin-phosphate-agar incubated for about ten days. Old cultures were transformed into a distinct coccus from which the original bacillus was again obtained on favorable media. This point has been considered by them as quite diagnostic of the *Corynebacterium granulomatosis maligni*. They have obtained it from all active cases. It is non-pathogenic to guinea-pigs and white rats, and at first did not take hold of the ape well, causing only transitory lymph-gland enlargement. They obtained a more virulent strain which caused the death of an ape in ten weeks, and from which the organism was recovered. Three other animals after repeated injections developed regional lymph-gland enlargement. The pathology of these glands resembled Hodgkin's disease in that there was a pronounced endothelial reaction, fibrosis, and sprinkling of eosinophiles, but there was also an extensive necrosis. These writers believe this picture corresponds to the early histology of Hodgkin's disease, the necrosis depending upon the virulence of the organism. According to the writer's experience this is not the picture early or late, and is not seen in the acutely toxic cases. In human histology necrosis is seen, but is rare and occurs only in small isolated foci.

In the literature there is considerable evidence advanced that the *Corynebacterium granulomatosis maligni* is the established cause of Hodgkin's disease. There is little if any literature describing these organisms as an accidental factor or as contaminations in the cultural work on Hodgkin's disease. The work I have done was an attempt to confirm the findings of others, and in connection with a study of all the cases that have been at the hospital in the last five years, hoping that something might be accomplished by the use of vaccines. Shortly after the onset of these observations a lymph gland was excised which appeared in the gross like Hodgkin's disease. A diphtheroid organism was isolated from this gland which proved

¹⁹ Arch. Int. Med., 1913, xv, 236.

²⁰ Jour. Am. Med. Assn., 1913, lxi, 1803.

²¹ Johns Hopkins Hosp. Bull., 1914, xxv, 173.

²² Ibid., 1914, lxii, 516.

²³ Ibid. p. 177.

on section to be tuberculous. Several other glands were cultivated, with the results enumerated below.

The work of Harris and Wade²⁴ has shown that the diphtheroids are widely disseminated and that many diseases were ascribed to these until the specific cause had later been found. Positive cultures to be of value should have control especially in the cultivation of tissues when the chance of contamination is great. The results of my own observations seem to confirm this. Glands that are not properly cared for may easily be contaminated and harbor the organism which "takes a three days' search to find" to recall the quotation of Fränkel and the reference of Bunting.

If Hodgkin's disease has been produced in the ape with certain cultures then there could be little doubt about the corynebacterium. Necrosis is uncommon in Hodgkin's disease and I dare say never the predominating picture; if such occurs other organisms must be associated. Necrosis is seen in the pyogenic infections, syphilis, tuberculosis, and neoplasms. There is also a reaction in lymph glands due to some type of irritation, showing itself as a pronounced endothelioid hyperplasia, in which the diagnosis without full clinical history is difficult. We know from the work of Blumer²⁵ that glands of status lymphaticus (bacterial-free?) injected into guinea-pigs will cause lymphatic necrosis, and from the work of Woltman²⁶ similar effects from foreign sera, etc., may be obtained. In this connection, however, we might say that emulsions of any tissue, bacterial-free, could cause such change a sort of anaphylactic reaction. We cannot say, however, that such reactions are not the results of action of the products of bacteria. Herein lies the etiology of the so-called irritative hyperplasia of lymph glands.

The following grouping is made purely on the grounds of technique in the cultivation. In the first group, glands removed in the operating room were brought to the laboratory in a sterile towel. Hereafter hastily boiling up the instruments used in gross pathological work some of the glands were mashed, others squeezed and planted on tubes of egg, glycerin-potato-agar and Loeffler. The result of this group is as follows:

GROUP I. *Case I.* (A) Cascons tuberculous glands. Cultures were made on blood-agar slants. At the end of forty-eight hours slight cloudiness was noted about the tissue and Gram's stain showed a plump bipolar rod with body of organism staining pink. Colonies were very small and tenacious. With Gabbet's stain the polar bodies were more resistant to acid. The organism remained as a bacillus throughout twelve days' observation.

(B) Glands from the opposite side of the neck two weeks later. In four days from glucose-agar slants a large and small Gram-

²⁴ Jour. Exper. Med., 1915, xxi, 493.

²⁵ Quoting Flexner, Johns Hopkins Hosp. Bull., 1903, xiv, 275.

²⁶ Jour. Exper. Med., 1905, vii, 119.

positive bacillus and coccus were isolated. Transplants gave a good growth of a Gram-positive pleomorphic rod. On Loeffler forms appeared more slender. Morphologically it is different from that isolated from the opposite side of the neck.

Case II. Caseous tuberculous glands. Cultures made on glucose serum agar and blood agar. In six days from serum-glucose-agar a short Gram-positive rod, bipolar, was isolated. Many coccoid forms were seen. Cultures eleven days old presented many clubbed forms. The younger cultures were similar to IA, but the older cultures showed many involution forms. One tube remained sterile.

Case III. Tuberculous lymph gland. Cultures made on aseptic glucose agar. Two tubes gave a pure culture of *Staphylococcus albus* and one tube a mixed culture of a short Gram-positive bacillus and coccus. It was impossible to isolate the bacillus, but the few seen showed no pleomorphism.

Case IV. Subleukemic lymphadenosis. Clinically and pathologically this was a very interesting case, but far from a typical Hodgkin's.²⁷ A gland was removed from the axilla and cultivated by Dr. Warren. A Gram-positive pleomorphic rod was isolated which became coccoid. It was transformed into a bacillus and recognized by Bunting as a typical *Bacillus hodgei*. Some of the other organisms isolated are very similar to this strain and have the same tendency to become coccoid, and these from glands definitely tuberculous.

Case V. Hodgkin's disease. Five tubes were inoculated and three gave a large Gram-positive coccus.

(a) Egg tube. Diphtheroid bacillus arranged in parallels, Gram-positive with body staining pink. It appeared first as a short bacillus but with subsequent cultivation on Loeffler the forms appeared longer and more slender. It remained as a bacillus throughout three weeks' observation. The young transplants appear very short, with rounded ends, and became distinctly pleomorphic.

(b) Glycerin-potato-agar. A short Gram-positive digastric bacillus was obtained. After seventy-two hours many small coccoid forms were seen. It later became contaminated.

Case VI. Large round-cell sarcoma, primary mediastinal. A supraclavicular gland was excised for diagnosis and cultivated on glycerin-potato-agar and egg media. From one tube was obtained a short Gram-positive bipolar rod with central constriction and from another a Gram-positive coccobacillus. On Loeffler the pleomorphism of the former was better made out and the forms were more slender. After several days' growth many cocci and coccoid forms were seen. Several other tuberculous glands were cultivated and a large coccus was obtained.

²⁷ Warren: Proc. New York Path. Soc., 1915, xv, No. 142.

While this work was in progress approximately 225 cultures were made in the wards, operating room, and laboratory, and diphtheroids were isolated several times. None, however, came from the operating-room cultures. One was from a culture taken from the heart's blood in the morgue. Dr. Warren called attention to the fact that there had been several periods at the hospital when diphtheroids were frequent contaminants in blood cultures. One of these periods followed shortly and several cultures after four to five days presented diphtheroids in the broth. We felt that our technic could be improved, so subsequent cultures were made in the Syms operating room carrying out aseptic technic to the minutest detail, with the following results:

GROUP II. Two cases of Hodgkin's disease, one cervical the other axillary; both showed rapid enlargement in the past few months. Glands from both these cases were cultivated on several tubes of egg and glycerin-potato-agar and remained sterile at the end of two months.

Four cases of tuberculosis:

(A) Soft caseous gland; all tubes gave a *Staphylococcus pyogenes albus*.

(B) Chronic tuberculous lymphadenitis; all tubes sterile at the end of month.

(C) Retroperitoneal gland (tuberculosis of ileum). Pure culture of *Bacillus coli* in two tubes; one tube remained sterile for three weeks.

(D) Endothelioid tubercenlosis. Four tubes remained sterile. One case of chronic cervical lymphadenitis, unclassified, but with a specific history, gave in two tubes a slowly growing streptococcus.

SUMMARY AND CONCLUSIONS. All these organisms may be placed in the diphtheroid group, and only on morphological grounds am I able to say that many of them are of different strains. The organisms which were isolated from glands of Hodgkin's disease, however, are very similar if not identical with those from the tuberculous glands. In Case I, cultures from glands on both sides of the neck, two weeks apart, gave somewhat different organisms, while that described from IA appeared like the organism isolated from Case II. In some instances the diphtheroids were primarily associated with cocci which later overgrew them.

It is reasonable to suppose that glands draining such places as the mouth, throat, and tonsils should harbor such organisms as are commonly found in these portals. With the evidence at hand, however, the occurrence of them in the laboratory, in blood cultures (appearing rather late), in the heart's blood at the morgue, in ascitic fluid, and in a series of gland cultures of questionable technic, and not in a series where technic is definitely controlled, I am led to believe that we are dealing with organisms whose natural habitat is the laboratory. The series is, however, too small to make

a positive statement, but I do not believe the organism heretofore described bears any relation to the cause of Hodgkin's disease.

I wish to acknowledge with thanks the courtesy of the attending staff in supplying me with the material and the suggestions and coöperation of Dr. Warren.

SOME PHYSIOLOGICAL EFFECTS OF VARIOUS ATMOSPHERIC CONDITIONS.¹

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ATMOSPHERIC environment is an interesting and important factor in many medical problems in which no group of physicians is more directly interested than are the members of the American Climatological and Clinical Association, and, moreover, no one in this country has contributed more than they to the advancement of this phase of medical knowledge.

It is for this reason and also as a result of my own recent experience for three years in the work of the New York State Commission on Ventilation that this topic has been chosen for presentation on this occasion.

It is my purpose to approach the subject more from the physiological point of view in the hope that by a consideration of certain fundamental principles a clearer vision may be afforded of the problems involved in the effect which atmospheric conditions exert upon the comfort and efficiency of mankind as well as of the role they may play in the causation, prevention, and treatment of disease.

The respiratory functions of air focussed the attention of physiologists for generations, in fact, until very recent years. Consequently its effect upon the human body was interpreted solely in respiratory terms and rules of hygiene were formulated upon this basis. Withindoors inadequate ventilation was gauged in terms of deficient oxygen or of excess of carbon dioxide, or later of the presence of certain volatile poisons in the air that was breathed. Outdoors the general effect in health and disease produced by variations in climate or of its temporary representative, the weather, was also ascribed solely to their influence upon the air we breathe. To the truthful part of this hypothesis we all pay fitting tribute in the joy of the full deep breath upon a fine, crisp morning.

Under the lead of Pettenkofer² the CO₂ content of the air was for

¹ President's address at the meeting of the American Climatological and Clinical Association, Washington, May 9 to 11, 1916.

² Liebig's Annalen, 1862-1863, Suppl., ii, 1.